REMARKS

Claims 1-12 are pending in this application. Claim 9 has been canceled. New claims 13-19 have been added. Claim 13 is a product-by-process claim dependent upon product claim 3 and finds support in original claims 1 and 3. Claim 14 is directed to a pharmaceutical composition comprising the immunoglobulin product according to claim 3. Claim 15 a product-by-process claim and substantially corresponds to claim 1 except that claim 15 does not specify in step (l) to add a saccharide to adjust the osmolality. Support for the amendment is found on page 18. Claim 16 further defines the infectious particles in claim 13. Claim 17 further defines the infectious particles in claim 1. Claim 18 substantially corresponds to claim 1 but also specifies that the immunoglobulin product has a IgA content of less than 6 mg/l (see page 21, line 10). Claim 19 substantially corresponds to claim 1 but also specifies that the immunoglobulin product has a content of polymers and aggregates of less than 5% (see page 21, lines18-24). No new matter has been added.

1. Specification

The Examiner indicated that the first paragraph of the Specification needed to be updated to reflect the correct status of the parent application. Applicant has amended the Specification accordingly. Reconsideration and removal of the objection is respectfully requested.

2. Claim Objections

The Examiner has objected to claims 1-2 and 11-12 because the word "agent" in step (j) is misspelled. Applicant has corrected the misspelling. Reconsideration and removal of the objection is requested.

3. Claim Rejections under 35 U.S.C. §112, second paragraph

The Examiner has rejected claims 1-2, 9 and 11-12 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Specifically, the Examiner has rejected claim 1 for the use of the phrase "such as". Applicant has amended the claim to delete this phrase and has added new dependent claim with this removed subject matter. The Examiner rejected claim 9 as an improper method claim. Applicant has canceled claim 9 thereby obviating the rejection.

Applicant believes that the foregoing amendments have overcome the indefiniteness rejections. Accordingly, reconsideration and removal of the rejection is respectfully requested.

4. Rejections under 35 U.S.C. §101

The Examiner rejected claim 9 under 35 U.S.C. §101. As noted above, this claim has been canceled rendering the rejection moot. Reconsideration and removal thereof is respectfully requested.

5. Rejections under 35 U.S.C. §102

The Examiner has rejected claims 1-2 and 11-12 under 35 U.S.C. §102(b) as being anticipated by Applicant's statements regarding the art, specifically the Octagam liquid formulation and/or any of Mollnes et al., Brenner or Biesert. The Examiner then argues that it is apparent that applicant is not the inventor of the instant invention in light of applicant's "admissions" and has also rejected these claims under 35 U.S.C. §102(f). The Examiner has also rejected claims 1-2 under 35 U.S.C. §102(b) as being anticipated by Doleschel et al. (US 4,880,913). Claims 1-10 have been rejected as anticipated under 35 U.S.C. §102(e) in view of Mamidi et al. (US 6,162,904). Applicant respectfully traverses. The specific rejections are discussed in more detail below.

A. Octagam and/or Mollnes et al., Brenner or Biesert

The Examiner has rejected claims 1-2 and 11-12 as being anticipated by the Octagam liquid formulation and/or any of Mollnes et al., Brenner or Biesert in view of Applicant's admissions. The Mollnes et al., Brenner and Biesert references were, for the most part, merely used to demonstrate that the Octagam product was available more than one year prior to applicant's filing date. Brenner was also cited for disclosing the use of Octagam to treat ITP. addressed the par The Examiner specifically refers to statements made on pages 19-22, 30 and in Example 2 and the Table on page 26 of the Specification. The Examiner then concludes that the obtained product in claim 1 is indistinguishable from the Octagam formulation based on review

of **4 of the 23** distinct parameters listed in the Table on page 26 of the Specification. Applicant respectfully disagrees.

The table on page 26 of the instant application demonstrates that the product according to the invention (IVIG, SSI) has a IgA content of 1.36 mg/l. The instant product is therefore distinguishable from the Octagam product, which has an IgA content of 54.7 mg/l (see Table of Example 22 on page 26 of the Specification). The data in the table also indicates that the content of IgM in the Octagam product is remarkably higher than the IVIG product according to the instant invention. Additional evidence supporting the differences between the claimed product and the Octagam product may be found on page 31 at line 3 where it states that the product of invention has improved stability as compared to the other liquid products analyzed which implies that the product is not identical to known liquid formulations.

It should also be noted that maintaining a low content of IgA is important. IgA deficiency is a very common immune-deficiency state with a prevalence of <0.3%. IVIG treatment of IgA deficient patients is known to contribute to serious anaphylactic reactions as side effects if the IgA content is too high. Until now, no commercial product with low IgA content has been available. Prior art process were unable to separate IgA from IgG because the molecular weight of IgA is almost identical to the molecular weight of IgG (160 kD compared to 146-165 kD for IgG). This makes it almost impossible to remove the IgA from a solution of IgG using e.g. HPLC. Thus, an IgG solution fractionated by HPLC will contain a large amount of IgA, making the product less desirable.

In view of the foregoing remarks, Applicant submits that the immunoglobulin product of claims 1-2 and 3-10 is clearly distinguishable from Octagam. With respect to the method of treatment claims 11-12, Applicant submits that the foregoing remarks also demonstrate that the teachings of Brenner et al. regarding the use of Octagam to treat ITP do not anticipate the present claims which are directed to treating ITP and other conditions using the immunoglobulin product according to claims 1 or 3. Applicant also submits that the 102(f) rejection in view of these references should also be dismissed, as it is evident that the present product is different from the

Octagam product. Accordingly, reconsideration and removal of the anticipation rejections in view of the Octagam formulation and/or any one of Mollnes et al., Brenner or Biesert is respectfully requested.

B. Doleschel et al. (US 4,880,913)

The Examiner has also rejected claims 1-12 as anticipated by Doleschel. The Examiner argues that the instant preparations cannot be distinguished from those of Doleschel in terms of purity, monomer/content and IgA content. The Examiner relies on information contained within the Table on page 26 of Applicant's Specification and the tables of Doleschel. The Examiner appears to be arguing that the Doleschel product inherently contains the same characteristics as the instant products (see para. 2 on page 6 of the Office Action). Applicant respectfully disagrees.

When the Examiner argues that the prior art product inherently possesses the same characteristics as the claimed invention, the burden shifts to the Applicant to demonstrate that the products are, in fact, different. Applicant submits that the immunoglobulin product of claim 1 and 3 can be distinguished from the product of Doleschel for the following reasons:

- **Higher content of unwanted PEG in the Doleschel product**

In the Doleschel examples, a PEG precipitation step is performed as the last purification step by adding 10% or 15% PEG 1000 and 600, respectively. The removal by ultrafiltration is described in example 1: through a Millipore cassette against five times the amount of glycine/NaCl buffer. When taking the lowest PEG addition of 10% equivalent to 100 mg/ml with ultrafiltration against five times the amount of buffer the PEG concentration will be diluted 2^5 times i.e. 32 times. The PEG concentration of the final immunoglobulin preparation will therefore be 3.1 mg/ml; this is a markedly higher content than the 0.02 mg/ml of the product of the present application.

• The gammaglobulin product disclosed in US 4,880,913 is not suitable for intravenous administration in liquid form

An immunoglobulin preparation to be used for intravenous administration as a medicinal product has to be produced by a large-scale process fulfilling the demands of good manufacturing practice and product safety. In the examples of Doleschel, the starting material is dissolved in demineralised water and dialyzed against running demineralized water for 2 days. Demineralized water cannot be used for the production of a plasma-derived product for intravenous use. Dialysis against running water also cannot be used in a manufacturing process of such a sterile therapeutic product nor is it compatible with a production on a large scale.

• The Doleschel Product Contains a Higher Content of unwanted IgA

The content of IgA is determined by the Ouchterlony technique, this method showing a much lower sensitivity, at least 100 fold lower than the ELISA used for IgA quantification in the present patent application. The IgA content in the preparations of Doleschel therefore, in reality, exceeds that of the products claimed in the present application.

• IgG subclass distribution

Different purification processes for IgG result in variations of the subclass distribution, especially with respect to the two small subclasses, IgG3 and IgG4. The Examiner's attention is directed to table 2 of the application where it is apparent that two of the analyzed IVIG products do not fall within the range of IgG4 recited in claim 6. The Examiner's assumption that the Doleschel products would necessarily contain the "normal" content of the four IgG subclasses corresponding to the percentage levels of claim 6 is misplaced.

• The ion-exchange steps in the production processes are different, which implies that the product of the present invention has a higher purity

The methods of Doleschel include one or two anion-exchange steps i.e. batch-wise adsorption of impurities at pH 6.0-9.0 by the addition of the ion-exchanger to the IgG

solution for subsequent removal by filtration. In the process of the present application two combined anion- and cation-exchange steps are included i.e. the IgG containing solution with a pH < 6.0 is applied to the serial connected anion- and cation-exchange resins. Consequently, protein impurities are retained on the anion-exchange resin and IgG on the cation-exchange resin, with subsequent elution and harvesting of IgG from the later. These two ion-exchange steps are different regarding the aspects of product purification and technical use in a large-scale process.

- **The methods of Doleschel do not include steps for virus reduction making the IgG preparations unsafe and unable to fulfill guideline demands for IVIG products.**

- **Doleschel does not teach a pH value or stability of a liquid product, the formulation might therefore result in an unstable product not usable for intravenous administration.**

The foregoing remarks demonstrate the various differences between the instant products and those described by Doleschel. Applicant submits that these remarks are sufficient to rebut the Examiner's assumptions regarding the inherent teachings of Doleschel. Reconsideration and removal of the anticipation rejection in view of the Doleschel reference is, therefore, respectfully requested.

C. Mamidi et al. (US 6,162,904)

The Examiner has rejected claims 1-10 under 35 U.S.C. §102(e) by Mamidi et al (US 6,162,904 and WO 99/33484). The Examiner argues that this reference discloses a product that is consistent with the product of claim 3. The Examiner also argues that the reference discloses the removal of PEG and albumin and hence has rejected claim 4. Claim 5 has been rejected because the IgA content is apparently disclosed in Mamidi. Claim 6 has been rejected because the Examiner assumes that the Mamidi composition inherently contains the "normal" levels of IgG4 recited in

claim 6. Claims 7-10 have been rejected because Mamidi allegedly teaches IV administration of a liquid product. Applicant respectfully traverses.

Although the process of Mamidi and the present application show similarities, the former process contains more steps and is technically more complicated to perform as it involves i.e. washing of paste II+III and precipitation, heat treatment, two PEG precipitation steps, bentonite addition, batch wise ion-exchange steps instead of column chromatography, anion- and cation steps separated and at different pH values. The use of polyethylene glycol as a protein-precipitating agent is known in the art of protein precipitation. A two-step PEG precipitation with collection of the purified immune globulin for subsequent suspension and pH equilibration before batch wise anion-exchange chromatography as taught by Mamidi is quite different from the process of the applied product. Here, impurities are precipitated in one step and the remaining viscous PEG supernatant is loaded directly onto serial connected anion- and cation-exchange columns in one step, to perform a purification on the anion-exchange column and a concentration of the purified IgG fraction by retention on and subsequent elution from the cation-exchange column.

The Examiner's assumptions on pages 6-7 are addressed below:

- The Applicant respectfully submits that the product of Mamidi is not consistent with the limits of claim 3 of the present application and/or the limit in the specification (page 21, lines 10-12, IgA less than 6 mg/l). In example 1, the content of IgA in Mamidi's product is 22 µg/ml which is equivalent to 22 mg/l and outside the scope of claim 3 of the present application. In example 2, the content of IgA in the Mamidi product is 78 µg/ml equivalent to 78 mg/L. This data demonstrate that the Mamidi product does not define a product that is consistent with the limits of claim 3.

- The Examiner has rejected claim 4 is rejected because Mamidi teaches PEG and albumin are removed. Applicant respectfully submits that claim 4, which is dependent on claim 3 of

the present invention which defines the content of IgA is defined as less than 4 mg/l, also makes claim 4 patentably distinct from Mamidi.

• Claim 5 is rejected since the IgA content of 22 µg/ml according to the Examiner converts to 2.2 mg/l (!). This is incorrect. The Applicant respectfully submits that 22 µg/ml converts to 22 mg/l and this is outside the limits of claim 5 (and the other claims) of the present application.

• Claim 6 was rejected using the same rationale applied to the Doleschel. Applicant believes that its remarks regarding the Doleschel's reference *supra* explain why it is not reasonable to assume that the Doleschel or the Mamidi references would contain the range of IgG1, IgG2, IgG3 or IgG4 recited in claim 6. The subclass distribution of the products of Mamidi is not shown and might very well be outside the ranges of claim 6 since the process consists of many steps including heat treatment and 2 PEG precipitations. However, Applicant respectfully submits that claim 6's dependency on claim 3 which specifies that the IgA should be below 4 mg/ml, renders it patentably distinct from Mamidi.

• Claim 7-10 are rejected since Mamidi teaches intravenous administration of a liquid product. Claims 7-10 all refer to a product according to claim 3, for which novelty has already been demonstrated in the foregoing remarks.

The foregoing remarks demonstrate the important differences between the claims 1-10 of the instant application and the products (and method) disclosed by Mamidi. Simply stated, the IVIG product of the present invention has an IgA content about 15 times lower than the IVIG product of Mamidi making it much safer for use in IgA deficient patient. Accordingly, reconsideration and removal of the anticipation rejection is respectfully requested.

Applicant has also added two new claims, 18 and 19, which further define claim 1 by specifying the content of IgA to be less than 6 mg/l (see page 21, line 10) and to specify that the content of polymers and aggregates are less than 0.5% (see page 21, lines 18-24). The products defined by new claims 18 and 19 are not disclosed or suggested by any of the cited prior art references. Applicant further submits that the above comments relating to claims 1 and 3 are also applicable to new claims 18 and 19 and demonstrate the novelty of these products in view of the prior art.

6. Rejections under 35 U.S.C. §103

The Examiner has rejected claims 1, 3 and 11-12 under 35 U.S.C. §102(b) as anticipated by, or in the alternative, under 35 U.S.C. §103(a) as obvious over Mamidi or Doleschel alone or in view of Applicant's own admissions. Applicant respectfully traverses.

Applicant has already addressed why these two references fail to anticipate the instant claims and new claims 18 and 19 and will, therefore, not repeat those comments here. Applicant further submits the instant products and method of the invention are not rendered obvious in view of the Mamidi or Doleschel references. As noted in the Specification, the inventors have surprisingly discovered that the product of the invention does not need addition of stabilizers such as detergents, PEG or albumin, in order to avoid aggregation of IgG during storage. It is contemplated that this unexpected advantage of the IVIG SSI product is due to the improved purity, and it was not foreseen by the person skilled in the art. (cf. the description page 4, lines 21-27, page 19, lines 15-19 and page 31, top). Moreover, as can be seen from the prior art cited by the Examiner, the known products having a low content of polymers and aggregates all contain stabilizers, and the Octagam product which contains albumin has a relatively high content of polymers and aggregates, as well as a high content of IgA and IgM. Thus, a IVIG product without said stabilizers and the use of these products to effectively treat various conditions (i.e. as in claims 11-12) would not be obvious to the skilled artisan. Reconsideration and removal of the obviousness rejection is respectfully requested.

Favorable consideration and early allowance of the claims is requested.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Leonard R. Svensson (Reg. No. 30,330) at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

Pursuant to 37 C.F.R. §§ 1.17 and 1.136(a), applicant(s) hereby petition(s) for an extension of time for three (3) months to May 27, 2003 for filing a reply to the Office Action dated November 27, 2002 in connection with the above-identified application. A check in the amount of $930.00.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail, postage prepaid, in an envelope to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on: May 22 2003
(Date of Deposit)

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Respectfully submitted,

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Attachments: Amendments to the Specification and Claims